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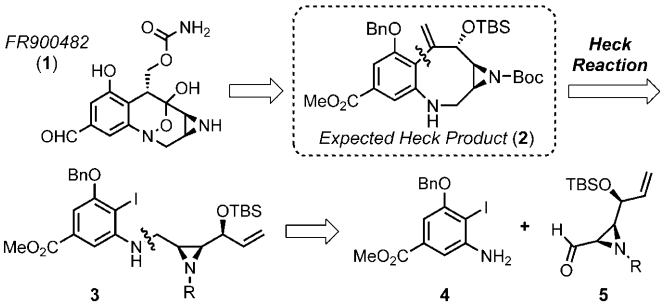
Investigation of a Domino Heck Reaction for the Rapid Synthesis of Bicyclic Natural Products

Barry M. Trost,*[a] Brendan M. O'Boyle,[b] and Daniel Hund[c]

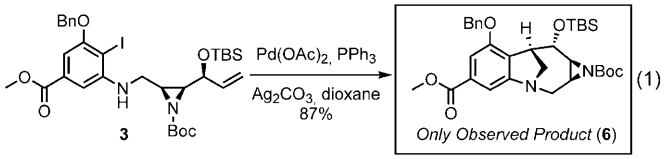
Dedicated to Professor José Barluenga on the occasion of his 70th birthday

The Heck reaction has proven to be an exceptionally useful tool for the construction of carbon–carbon bonds. The traditional Heck reaction consists of oxidative addition by palladium(0) to a carbon–halogen bond, followed by migratory insertion into a carbon–carbon π-system and finally β-hydrogen elimination. A number of clever domino reactions[1] have been implemented using either sequential Heck reactions[2] or an initial Heck reaction in tandem with another palladium catalyzed process.[3]

During efforts toward the synthesis of FR900482,[4] we intended to utilize an 8-*exo-trig* Heck reaction to forge the benzazacine core of the molecule (Scheme 1). Instead when **3** was exposed to Heck reaction conditions[5] a remarkable result was obtained. Rather than the expected exocyclic olefin **2**, bicycle **6** was formed in remarkable yield with no trace of the expected Heck product [Eq. (1)]. This result represented an unprecedented domino Heck/alkylation, even in the presence of geometrically accessible β-hydrogen atoms. We were intrigued by this demonstration that β-hydrogen elimination may not always be kinetically preferred over alternative terminating steps. This possibility would open many alternative synthetic disconnections if it could be employed in a predictable manner.



Scheme 1. Synthetic planning toward (+)-FR900482 utilizing a Heck coupling.



Several mechanistic scenarios could account for this remarkable transformation (Scheme 2). We believe the most likely mechanism for the observed product is oxidative addition of Pd^0 to the carbon–iodine bond of **3** yielding **3a**, followed by migratory insertion through an 8-*exo-trig* pathway to afford intermediate **3d**. Rather than the expected β-hydrogen elimination, which is not geometrically inaccessible, a transannular alkylation reaction ensued. This most likely occurs by nucleophilic displacement of palladium by nitrogen, which regenerated the Pd^0 catalyst and yielded tetracycle **6**. A reductive elimination pathway to form the C–N bond is also conceivable, however, the lack of reported C–N reductive elimination with this catalyst system causes us to favor an alkylation pathway. The surprising reluctance of **3d**

[a] Prof. B. M. Trost
Department of Chemistry, Stanford University
Stanford, CA 94305-5080 (USA)
Fax: (+1)650-725-0002
E-mail: bmtrost@stanford.edu

[b] Dr. B. M. O'Boyle
Merck Research Laboratories:
BMB 3-114, 33 Avenue Louis Pasteur
Boston, MA 02115 (USA)

[c] D. Hund
Institute of Inorganic and Analytical Chemistry
University Freiburg, Albertstrasse 21
77871 Freiburg (Germany)

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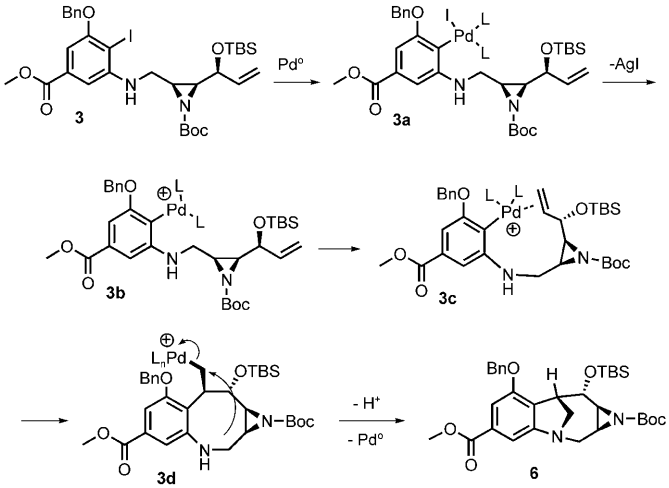
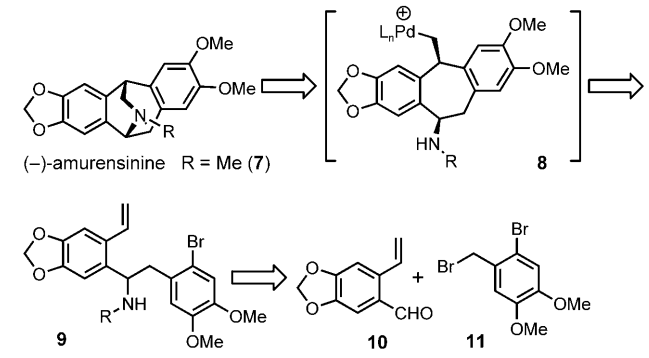


Scheme 2. Mechanism of the unexpected domino-Heck alkylation reaction.

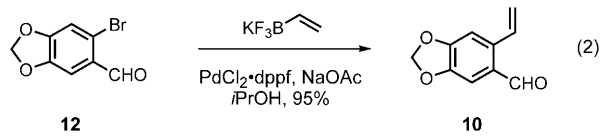
to participate in β-hydrogen elimination is convincing evidence that the relative rate of the elimination is dramatically less than that of alkylation. The former may be hindered by the bulky groups flanking palladium in **3d**, which inhibit the requisite *syn* conformation between palladium and the benzylic hydrogen needed for elimination to occur. Also, the conformation of **3d** may enhance the rate of alkylation. Within an 8-membered ring transannular events are particularly favorable, which may further bias the reaction toward bicycle formation.

The above result is reminiscent of the work of Grigg,[6] in which similar organopalladium intermediates underwent substitution with nucleophiles, such as acetate and cyanide. To the best of our knowledge, no previous reactions of this type have been reported when geometrically accessible β-hydrogen atoms were present. We were intrigued by the potential synthetic impact of this domino-Heck methodology. To test whether the reaction could be extended to other systems, we devised a synthetic approach to amurensinine (**7**),[7,8] that relied on this domino-Heck reaction manifold as a key step (Scheme 3).

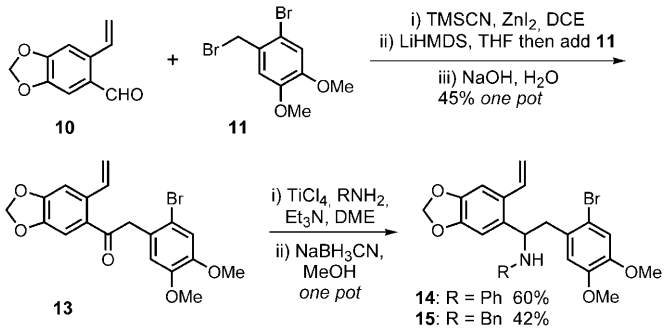


Scheme 3. Proposed domino-Heck reaction.

Disconnection of the indicated carbon–nitrogen bond of **7** would lead to organopalladium intermediate **8** prior to transannular alkylation (Scheme 3). Bromide **9** would then represent the immediate precursor to the natural product, and could be accessed in a few steps from aromatic fragments, such as **10** and **11**. These fragments were easily prepared through a known procedure for **11** and through a Molander/Suzuki[9] coupling between commercially available potassium vinyltetrafluoroborate and 5-bromopiperanal (**12**, [Eq. (2)]).



With fragments **10** and **11** in hand, efforts turned toward completion of the domino-Heck substrate (Scheme 4). Monometallation of bis-bromide **11** in the presence of magnesium proved more difficult than expected. Barbier conditions



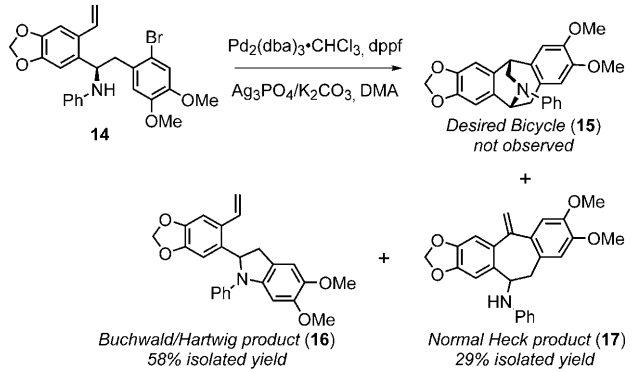
Scheme 4. Preparation of the domino-Heck substrate.

(In^0, NH_4Cl (aq), THF) failed to provide the desired product as well, as did Nozaki–Hiyama–Kishi conditions ($CrCl_2$, $NiCl_2$, DMSO). Particularly in light of the eventual need for an asymmetric synthesis, an umpolung coupling with an acyl anion equivalent, followed by reductive amination appeared to be a promising alternative. Formation of the trimethylsilylcyanohydrin (**10**, cat. ZnI_2, trimethylsilylcyanide (TMSCN), 1,2-dichloroethane (DCE)) was accomplished in excellent yield. Metallation, coupling, and base induced cleavage of the cyanohydrin were accomplished in one pot yielding benzylic ketone **13**.

Installation of the amino group was attempted by reduction and nucleophilic substitution (1. $NaBH_4$, MeOH; 2. PPh_3Br_2, $PhNH_2$, THF). Unfortunately, only elimination resulted in this case or with mesylation and attempted nucleophilic substitution. Low reactivity was observed under typical reductive amination conditions ($NaBH_3CN$, MeOH, AcOH, $PhNH_2$). However, forcing conditions ($TiCl_4$, $PhNH_2$, Et_3N, 1,2-dimethoxyethane (DME)) finally remedied the problem and provided either the *N*-phenyl or

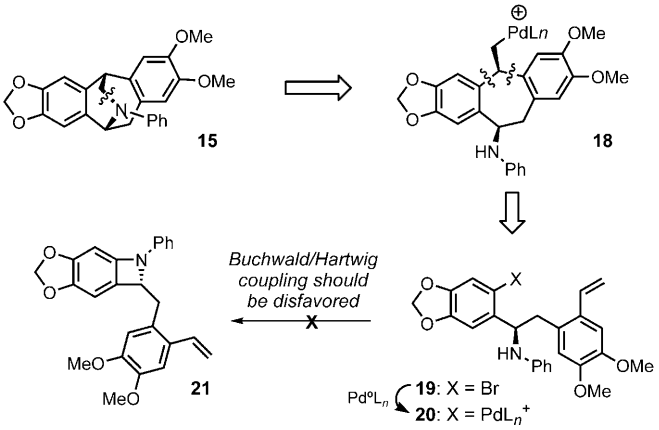
benzyl substituted secondary amines (**14** and **15**). It was envisioned that the phenyl group could be readily cleaved with methylation under the conditions reported by MacMillan and co-workers.[10]

With **14** and **15** in hand, attention turned toward the crucial domino-Heck reaction. Conditions completely analogous to the successful formation of **2** failed entirely due to complete oxidative decomposition of the starting material in the presence of silver(I)carbonate. Fortunately, use of the less oxidizing silver phosphate alleviated this problem and good conversion and recovery could be obtained. Unfortunately, the best conditions examined gave a mixture of the normal Heck product and the Buchwald/Hartwig product in a combined 87% yield (Scheme 5). Moving to more electron-withdrawing ligands was envisioned to disfavor the Buchwald/Hartwig coupling and hopefully speed the rate of transannular nucleophilic alkylation. However, no conversion was witnessed under these reaction conditions.



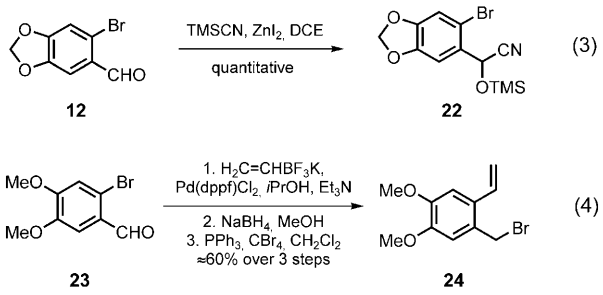
Scheme 5. Attempted domino Heck/alkylation reaction.

At this point, an alternative disconnection was investigated (Scheme 6). Transposition of the vinyl and bromo substituents on the domino-Heck substrate would produce organopalladium intermediate **18** directly from bromide **15** after oxidative addition. Through this alteration, Buchwald/Hartwig coupling should be disfavored due to the ring strain of **21**. Furthermore, one possible explanation for the formation of the normal Heck product would be if the amino and organopalladium intermediate were *trans* to one another yielding *epi*-**18** after migratory insertion. As the amine in intermediate **20** might be more disposed to coordinate to palladium, it seemed possible that this Heck reaction might have a better chance for success.

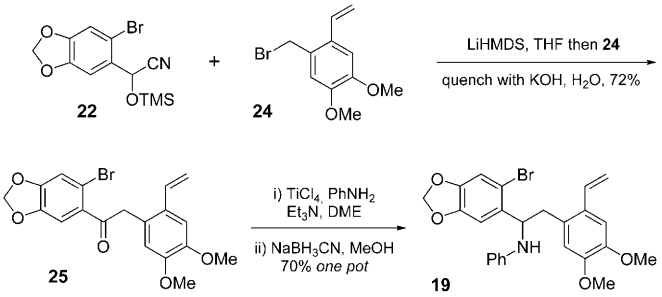


Scheme 6. Rethinking the domino-Heck reaction.

To test this possibility cyanohydrin **22** and benzyl bromide **24** were prepared [Eq. (3) and (4)]. It proved to be beneficial to the yield of the umpolung coupling to purify **22** through filtration through a plug of Fluorosil.

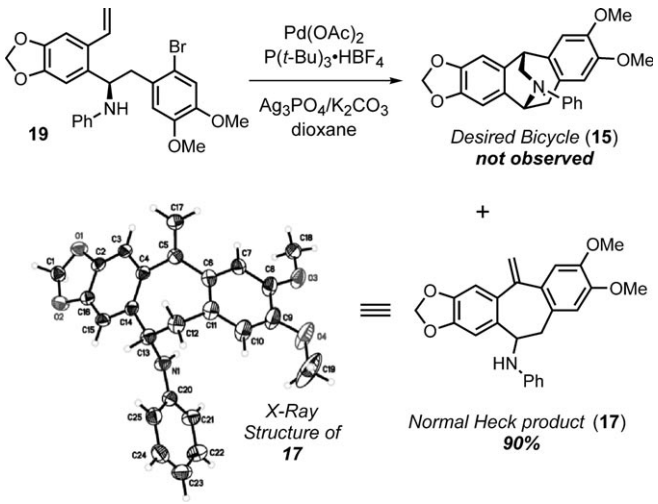


Benzyl bromide **24** was quite sensitive to decomposition, but could be isolated without special precaution so long as it was immediately used in the umpolung coupling (Scheme 7). The corresponding benzylic ketone **25** was prepared in an analogous manner as before. Reductive amination gave amine **19** in superior yield to the previous example.



Scheme 7. Preparation of a second domino-Heck substrate.

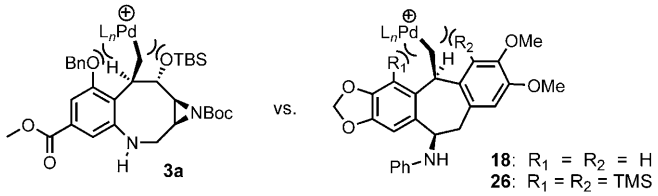
The domino-Heck reaction was reinvestigated employing **19** as the substrate. Qualitatively, it seemed that this substrate was more sluggish in the Heck reaction. Employing the optimal conditions from the previous example or [$PdCl_2$•dppf] (dppf = 1,1′-bis(diphenylphosphino)ferrocene) failed to give appreciable conversion. Palladium bis(triphenylphosphinedichloride) gave only slight conversion to the same normal Heck product as before. Only palladium(II)acetate with tri(*tert*-butyl)phosphine tetrafluoroborate adduct gave a good yield, again for the normal Heck product (Scheme 8). The Buchwald/Hartwig coupling product that



Scheme 8. Preparation of a second domino-Heck substrate.

had dominated in the previous substrate was not observed. The structure of **17** was confirmed through X-ray diffraction analysis. Although completion of the synthesis through **17** probably could have been accomplished, pursuing this task failed to address the real purpose of this methodology study.

The source of the difference in product distribution when **3** was employed under Heck conditions versus when **14**, **15**, or **19** were employed may be manifold. The simplest explanation is that the requisite *cis* stereochemistry between palladium and the amine required for alkylation was not formed. It is also possible that **18** was formed, but that a lower barrier for a co-planar conformation was required for the β-hydrogen elimination than was the case for **3a** due to lessened steric hindrance limiting the formation of the requisite co-planer relationship between the C–Pd and C–H bonds (Scheme 9). Analysis of **3a**, the organopalladium intermedi-



Scheme 9. Comparing successful and unsuccessful domino-Heck substrates.

ate responsible for formation of **2**, reveals that there are likely to be significant non-bonding interactions between the groups flanking palladium, which may explain the difference in the competitive rates for β-hydrogen elimination versus alkylation. Although intermediate **18** was envisioned to have hindered rotation as well, it is apparent from experimental evidence that this was not the case or alternatively that the epimeric organopalladium intermediate may be favored, causing the C–N bond formation to be geometrically inaccessible. Incorporating trimethylsilyl groups (**26**), might favor the desired product formation, although modification of the substrate in this manner would not be trivial.

In conclusion, we report the first example of an abnormal domino-Heck alkylation reaction in which geometrically accessible β-hydrogen elimination does not occur. This finding is significant because the underlying assumption that the Heck reaction must terminate in β-elimination greatly limits the possible synthetic scope of the process. Although our attempt to employ this reaction in the synthesis of amurensinine (**7**) has not yet proved fruitful, sufficient understanding of the Heck reaction would provide access to such polycyclic structures in a streamlined and atom economical[11] manner. To successfully implement this reaction manifold, greater understanding must be obtained concerning the factors that govern the relative rates of multiple possible terminating elementary steps. For example, is the failure of **19** to participate in the desired alkylation most strongly influenced by the conformation of intermediate **18**? Perhaps alternate ligands or nitrogen protecting groups would positively impact formation of the desired product rather than the normal Heck product. Or perhaps only in the presence of suitable coordinating or flanking groups (compare **18** and **26**, Scheme 9) will the desired reaction prove feasible.

Further investigation is certainly warranted to delineate these factors. In a similar vein, Fu's[12] extension of the scope of Suzuki coupling to sp^3–sp^3 systems has proven pivotal in opening new synthetic disconnections and furthering understanding of organometallic chemistry required for carbon–carbon bond construction. This development was accomplished by challenging conventional assumptions regarding the Suzuki reaction. A similar approach to the Heck reaction is likely to provide similar rewards.

Experimental Section

Tetracycle 6: A dry flask was charged with **3** (184.7 mg, 0.26 mmoles), palladium acetate (5.9 mg, 26 μmoles), triphenyphosphine (33.4 mg, 0.104 mmoles) and silver carbonate (144.3 mg, 0.522 mmoles). Freshly distilled dioxane was injected (7 mL) and the reaction was warmed to 60 °C in an oil bath. After 3 h the starting material was consumed as determined by TLC analysis (8:1:1 petroleum ether/EtOAc/CH_2Cl_2) and the fact that a significant amount of palladium black had precipitated from the reaction mixture. The reaction was allowed to cool to ambient temperature and filtered though a plug of Celite. The filter cake was washed with ethyl acetate and the combined filtrate was concentrated under reduced pressure. Flash chromatography (85:10:5 hexane/ethyl acetate/CH_2Cl_2) gave tetracycle **6** as a clear oil (132.7 mg, 87 %). $[\alpha]_D = -7.2°$ ($c = 0.32$, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$): $\delta = 7.42$–7.30 (m, 5H), 7.10 (d, 1H, $J = 1.2$ Hz), 6.85 (d, 1H, $J = 1.2$ Hz), 5.14–5.09 (m, 2H), 4.04 (d, 1H, $J = 8.4$ Hz), 4.01 (d, 1H, $J = 12.6$ Hz), 3.87 (s, 3H), 3.27 (dd, 1H, $J = 8.4$, 16.2 Hz), 3.02 (ddd, 1H, $J = 8.4$, 8.4, 10.8 Hz), 2.94 (dd, 1H, $J = 2.4$, 10.2 Hz), 2.84 (dd, 1H, $J = 1.8$, 6.6 Hz), 2.65 (d, 1H, $J = 6.0$ Hz), 2.51 (dd, 1H, $J = 11.0$, 16.2 Hz), 1.44 (s, 9H), 0.95 (s, 9H), 0.21–0.17 ppm (d, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 167.8$, 161.8, 155.2, 153.7, 137.6, 131.5, 129.1, 128.5, 128.0, 122.2, 106.5, 103.3, 82.1, 72.0, 70.8, 68.1, 52.7, 45.4, 43.4, 37.3, 32.2, 28.6, 26.4, 15.5, −3.6, −4.1 ppm; IR (neat): $\tilde{\nu} =$ 2954, 2931, 2857, 1722 (sharp) cm^{-1}; HRMS (EI$^+$): m/z: calcd for $[C_{32}H_{44}N_2NaO_6Si]^+$: 580.2969; found: 580.2968.

Normal Heck product 17: A flask containing **19** (22.0 mg), silver carbonate (7.0 mg), potassium carbonate (9.4 mg), palladium acetate (0.9 mg)

and tri(*tert*-butyl)phosphine tetrafluroborate (1.7 mg) was charged with dry dioxane (1 mL) and stirred at 100 °C for 18 h. After cooling to ambient temperature, the reaction was diluted with EtOAc and water. The organic phase was washed with water once more, and dried over magnesium sulfate. The crude product was purified by flash chromatography (3% EtOAc in toluene) to give **17** as a white solid (16.5 mg, 90%). ^{1}H NMR (500 MHz, $CDCl_3$): $\delta = 7.20$–7.10 (m, 2H), 6.90–6.60 (m, 6H), 6.65 (s, 1H), 5.95 (d, $J = 10.5$ Hz, 2H), 5.42 (d, $J = 1.2$ Hz, 1H), 5.40 (d, $J = 1.2$ Hz, 1H), 4.95–4.90 (m, 1H), 3.87 (s, 3H), 3.83 (s, 3H), 3.38–3.18 ppm (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 150.6$, 148.3, 147.3, 146.8, 146.5, 133.9, 132.7, 129.3, 128.9, 128.6, 126.4, 117.6, 116.5, 113.7, 112.9, 111.2, 108.5, 108.2, 101.0, 56.0, 55.9, 53.9, 37.8 ppm; IR (thin film): $\tilde{\nu} = 3392$, 2908, 1601, 1505, 1481, 1237 cm^{-1}; HRMS (ESI$^+$): *m*/*z*: calcd for $C_{25}H_{24}NO_4$: 402.1627 $[M+H]^+$; found: 402.1620.

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Keywords: amurensinine · domino reactions · Heck reaction · palladium · synthetic methods

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